Detailed Action

Applicant's response to restriction requirement of 03/06/2008 and Applicant's response to supplemental restriction requirement of 02-07-2008 have been entered.

Claim status. Claims 1-26 and 30-40 are currently pending. Claims 18-26 have been amended and claims 30-40 have been added by Applicant's amendment filed on 03-06-2008. Applicant's election of Group II, drawn to a method for inhibiting growth of cancers comprising administering a cell-containing preparation comprising a DNA sequence and a fibrous protein, i.e. claims 30-40 of Applicant's amendment filed on 03-06-2008, is acknowledged. Applicant further elected SEQ ID No. 2. Election of the following species in Applicant's response filed on 03-06-2008 is acknowledged: An epithelial cell of the oral mucosa as recited in claim 31, and an Adeno-associated virus (AAV) as recited in claim 36. Claims 1-26 are withdrawn for further consideration pursuant to 37CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Election was made **without traverse** in the replies filed on 11-05-2007 and 03-06-2008.

The requirement is still deemed proper and is therefore made FINAL.

Therefore, claims 30-40 are currently being examined to which the following grounds of rejection apply.

Information Disclosure Statement

1. The information disclosure statement filed on February 17, 2006 has been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

2. The information disclosure statement filed on February 17, 2006 fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Reference AK has been considered to the extent that an English Abstract has been provided. The following references were not considered for the reasons described below:

a) Reference AL is incomplete in the absence of translation,
b) Reference AM is incomplete in the absence of translation, and
c) Reference AO is incomplete in the absence of translation

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified untranslated copy of the foreign application PCT/JP2004/000630 has been filed on 12-06-2005.

Objections to the Specification

The disclosure is objected to because of the following informalities:

At page 9, line 27, the sentence reciting "NK4 secreted from into which Ad-NK4 is introduced is grammatically incorrect. Appropriate correction is required.

The specification recites at page 9, lines 24, the abbreviation "OMEC". The abbreviation has not been spelled out in the specification as-filed. The term should be spelled out in full at its first occurrence for clarity.

Appropriate correction is required.

The disclosure is objected to because of the following informalities: the specification does not comply with 37 CFR 1.821(d). At page 30, lines 27-29, the specification discloses one nucleotide sequence that have not been identified by their assigned SEQ ID NO.

Appropriate correction is required.

At pages 10 and 22, lines 11 and 28, respectively, of the as-filed specification, the use of the trademark VICRYL ™ has been noted. At page 12, lines 21- 22 of the as-filed specification, the use of the trademark Mutant-K ™ –superExpress Km and Mutant-K ™ -K , respectively, has been noted. At page 20, line 18, of the as-filed specification, the use of the trademark High Five ™ has been noted. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which may affect their validity as trademarks.

Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting growth, invasion and metastasis of cancer or for

inhibiting angiogenesis, which comprises administering a cell-containing preparation comprising a cell which has a DNA as set forth in SEQ ID NO:2, which encodes a mature human NK4 polypeptide, does not reasonably provide enablement for other fragments or variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims, when given the broadest possible interpretation, encompass a genus of fragments with any degree of homology to the sequence identified as SEQ ID No. 2. Additionally, the claims are broadly interpreted as comprising any size fragment and/or variants of a base sequence that hybridizes with SEQ ID No. 2 with the contemplated functionality of inhibiting metastasis of cancer or angiogenesis.

The specification provides insufficient data to enable claims directed to the fragments and/or variants of SEQ ID No. 2 as broadly claimed. Thereby, specific issues including the

functional limitations of DNA base sequences of any undetermined length with any degree of identity to SEQ ID NO. 2 that read on a genus of functional DNA able to exhibit an anti-tumor and an anti-angiogenesis activity, possibly because of by its antagonism of the c-Met/HGF receptor, have to be examined and considered for patentability regarding the broadly claimed DNA base sequences.

The specification as filed discloses at page 30, the preparation and cloning into replication deficient Ad-NK4 expression vectors of the NK4 cDNA isolated from subcutaneous tissue Rats by using the primers identified as SEQ ID:5 and SEQ ID No. 6. Additionally, rat oral mucosal epithelial cells (OMEC) harvested and grown on a biodegradable collagen membrane were transfected with the Ad-NK4 (p. 33, lines 1-26). Cancerous mass were induced in mice and the effect of NK-4-sheets comprising the adenoviral-transduced OMEC was assessed in relation to growth and angiogenesis of s.c. tumors (Example 3). The specification is silent about cloning of any other fragments and/or variants with any degree of identity to the nucleotide sequence of SEQ ID No. 2. Applicant has provided little or no guidance beyond the mere enumeration of sequences hybridizable with a DNA having a base sequence represented by SEQ ID NO:1 or 2 under stringent conditions (p. 6, lines 25-29) to enable one of ordinary skill in the art to determine, without undue experimentation, the fragments and/or positions in the SEQ ID NO:2, which encodes a mature human NK4 polypeptide, which are tolerant to changes (e.g. by nucleotide substitutions or deletions), and the nature and extent of changes that can be made in these positions.

The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of

its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence (e.g., SEQ ID No. 2) and that encode a polypeptide (e.g., SEQ ID No. 4) at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specified activity. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein cannot be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a NK4 than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

In terms of the structural requirements of the nucleic acid molecules, claims 30-40 recite an arbitrary structural relationship between the claimed nucleic acid sequence(s) and the single disclosed species of nucleotide sequence and amino acid sequence, respectively, based upon hybridization of nucleic acid. Hybridization of two nucleic acids, even under high stringency

conditions, requires only that the two nucleic acids share between 25 and 50 nucleotides in common. (Kennell, Progr Nucleic Acid Res. Mol. Biol. 11: 259-301, 1971, at the paragraph bridging pages 260-261). Such a sequence encodes only 8-16 amino acids. Consequently the claims embrace polypeptides that could share as few as 8-16 contiguous amino acids in common out of the 442 amino acids of SEQ ID NO: 4. Conversely, a nucleotide sequence that differs in every wobble base from SEQ ID NO: 2, for example, would encode SEQ ID NO: 4, but would not detectably hybridize to SEQ ID NO: 2 under any conditions. Thus, the recited structural relationship is arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at the nucleotide level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to SEQ ID NO: 2 or that encodes a polypeptide that is not 100% identical to SEQ ID NO: 4.

In the instant case, applicants only disclose two sequences, namely, the full length of SEQ ID No. 1 encoding the mature polypeptide NK4 of SEQ ID No. 3, and the full length of SEQ ID No. 2 encoding for mature polypeptide NK4 wherein the coding sequence for amino acids 131-135 of the SEQ ID No. 3 are deleted. Applicants provide no disclosure of what structural feature(s) of the instantly disclosed NK4 are responsible for the observed inhibition of metastasis of cancer or angiogenesis. Given the diversity of the claimed fragments and/or variants of SEQ ID No. 2, it is incumbent upon the specification to disclose means for identifying such variants commensurate in scope with coverage sought by the claims.

As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it

would have required undue experimentation to practice the instant invention to identify an enormous number of methods as broadly or generically claimed, with a resultant identification of a diversity of DNA sequences of any % identity or homology to SEQ ID NO. 2 exhibiting the biological activity of a mature NK4 of inhibiting growth, invasion and metastasis of cancer or for inhibiting angiogenesis in a mammal as broadly claimed.

Claim Rejections - 35 USC § 103

The instant claims are drawn to a method for inhibiting growth and metastasis of cancer cells in a mammal by administration of a cell-containing preparation comprising cells containing a DNA having a base sequence of SEQ ID NO: 2, which encodes a mature NK4 polypeptide fragment of HGF or any DNA sequence fragment able to hybridize under stringent conditions to SEQ ID NO: 2 and a fibrous protein. A DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 2 under stringent condition is broadly interpreted as any DNA fragment sequences that hybridize to any portion of SEQ ID No. 2 , for example, a base sequence that comprises a sequence complementary to SEQ ID No. 1.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30, 32, and 34-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., EP 1074264, Nakamura, T., WO 99/55361 and Seki et al. (Biochem. Biophys. Res. Commun. 172(1): 321-327, 1990; hereafter Seki-A).

Folkman et al., teaches methods for treating cancer by *in vivo* gene therapy involving administration of DNA encoding a kringle protein that inhibits angiogenesis, metastasis and proliferation, particularly angiostatin (col. 4, lines 33-49; col.5, lines 5-12; col. 30, lines 20-23). Although Folkman focuses primarily on angiostatin, it teaches that kringle regions of other proteins, including **hepatocyte growth factor (HGF)** or scatter factor, or nucleic acids encoding the same can be used (col. 6, lines 7-24, 28-30, and 57-59; col. 12, lines 60-65, col. 49, lines 15-35). Furthermore, in addition to *in vivo* gene therapy, Folkman teaches that *ex vivo* gene therapy may be used, where a cell is removed from the patient, transformed with a vector encoding the kringle protein and expanded, and then the transformed cells implanted back into the patient for expression of the gene product protein (col. 13, line 44; col. 14, lines 30-34). Additionally,

Folkman et al., teaches combinations with therapeutic compositions such as collagen matrix (col. 21; lines 10-15, 20 and 28). (Current **claims 30, 32, 34, and 37)** and matrices made from biocompatible materials such polyglycolide (polymer of glycolic acid)(col. 11, line 53; col. 21, lines 26-36)(Current **claims 38 and 39).** In addition, Folkman et al., teaches viral vectors for use in gene therapy protocols including adeno-associated virus (col. 15, lines 30-31)(current **claim 36**).

Folkman et al., does not teach a cell having a fragment of a base sequence encoding an NK4 fragment of **HGF** as the anti-angiogenic factor.

However, at the time the invention was made, Kuba et al., discloses that human NK4 protein functions as an anti-tumor agent not only as an anti-angiogenesis factor, but also by its antagonism of the c-Met/HGF receptor independent of its anti-angiogenic activity. It is suggested that blockade of this receptor was responsible for the inhibition of metastasis by NK4 administration. Kuba further discloses that NK4 has significant structural similarity to angiostatin (Abstract and pp. 6741-6742). In addition, Nakamura, EP 1074264 (and WO 99/55361), discloses methods for inhibiting neovascularization using human NK4 polypeptides, exemplified by SEQ ID NO: 1 and 2. The EP document does not include the Sequence Listing; however, this EP application is the EP national phase application of WO 99/55361, which does include the Sequence Listing. The two polypeptides of Nakamura exemplified by SEQ ID NO: 1 and 2 are the same as instant SEQ ID NOs: 3 and 4, respectively, except that the Gln residue at position 1 is shown as PyrGlu (p. 7, paragraph [0025]). Nakamura discloses that cDNAs encoding the HGF polypeptides upon which the NK4 polypeptides are based were as disclosed by Seki-A. **(**See entire document, especially cols. 3-4, 7-8, 12, and 13). Seki-A discloses cDNAs

encoding two isoforms of human HGF (Fig. 2), a long isoform HGF/NK4, that corresponds to instant SEQ ID NO: 1, and a shorter isoform, HGF/NK4(del 5), where the coding sequence for amino acids 131-135 of the long NK4 are deleted (corresponds to nucleotide 483-497 and amino acids 162-166 in prepro-HGF or pre-NK4) that corresponds to instant SEQ ID NO: 2. The NK4 coding regions of the long and short cDNAs of Seki-A, i.e. nucleotides 94-1434 (long) and 94-482 plus 498-1434 (short), are identical to instant SEQ ID NOs: 1 and 2, respectively. Seki-A also taught that the sequence difference between the isoforms of human HGF did not appear to affect its HGF activity (pp. 323 and 326).

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have used a DNA encoding the human HGF/NK4(del 5) of Nakamura (i.e. instant SEQ ID NO: 4 encoded by instant SEQ ID NO: 2) as the anti-angiogenic factor in the cell method of Folkman et al., comprising transformed cells and a fibrous protein. Kuba taught that human NK4 was structurally and functionally very similar to angiostatin, exemplified by Folkman, and like angiostatin, was an anti-angiogenic polypeptide. In addition to its anti-angiogenic properties, Kuba taught that NK4 was an antagonist of c-Met/HGF receptor, which activity may have been responsible for its activity in inhibiting metastasis. Nakamura taught that either of the two isoforms of human NK4, i.e. those of instant SEQ ID NOs: 1 and 2, were equivalents for use in inhibiting angiogenesis. Thus, Folkman, Kuba, and Nakamura, show that both NK4 isoforms are both structural and functional homologs to angiostatin, and additionally inhibit metastasis, possibly mediated by its antagonism of the c-Met/HGF receptor. The structural and functional similarity to angiostatin and additional antagonist activity would have suggested that the NK4 isoforms, including that of instant SEQ ID NO: 4 encoded by instant

SEQ ID NO: 2, were suitable in the method taught by Folkman, and had additional anti-tumor properties.

Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., EP 1074264, Nakamura, T., WO 99/55361 and Seki et al. (Biochem. Biophys. Res. Commun. 172(1): 321-327, 1990; hereafter Seki-A) as applied to claims 30, 32, and 34-39 above and further in view of Allen et al., , US Patent 7,115,256 (Date of Patent, Oct. 3, 2006) .

The teachings of Folkman et al., Kuba et al. Nakamura, T. and Seki are outlined in the paragraph above. The combined references fail to teach that cells are deposited on the surface of the fibrous protein.

However, at the time the invention was made, Allen et al., discloses methods of treating psychiatric disorders by application to selected sites in the brain where healing is desired of genetically engineered cells coating the surface of a support matrix, said cells able to produce dopamine (col. 3, lines 10-15; col. 4, lines 10-13; col. 12, lines 55-60; col. 13, line 64; col. 14, lines 1-7). Additionally, Allen et al., discloses support matrices made of collagen (col. 12, line 39). Furthermore, Allen et al., teaches that therapeutic cells of the invention may also be implanted or injected with support cells which improve the viability of the therapeutic cells (col. 6, lines 25-27; col. 7, lines 48-50; col. 12, lines 13-14). Although Allen focuses primarily on therapeutic cells adhered to a support matrix which produce dopamine, it teaches that cells can be genetically modified to produce other genes of interest (col. 10, lines 55-67 bridging to col. 11 lines 1-20).

Therefore, it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to have used a DNA encoding the human HGF/NK4(del 5) of Nakamura (i.e. instant SEQ ID NO: 4 encoded by instant SEQ ID NO: 2) as the anti-angiogenic factor in the cell method of Folkman et al., comprising transformed cells and a matrix of collagen. Kuba taught that human NK4 was structurally and functionally very similar to angiostatin, exemplified by Folkman, and like angiostatin, was an anti-angiogenic polypeptide. In addition to its anti-angiogenic properties, Kuba taught that NK4 was an antagonist of c-Met/HGF receptor, which activity may have been responsible for its activity in inhibiting metastasis. Nakamura taught that either of the two isoforms of human NK4, i.e. those of instant SEQ ID NOs: 1 and 2 were equivalents for use in inhibiting angiogenesis. Thus, Folkman, Kuba, and Nakamura, show that both NK4 isoforms are both structural and functional homologs to angiostatin, and additionally inhibit metastasis, possibly mediated by its antagonism of the c-Met/HGF receptor. The structural and functional similarity to angiostatin and additional antagonist activity would have suggested that the NK4 isoforms, including that of instant SEQ ID NO: 4 encoded by instant SEQ ID NO: 2, were suitable in the method taught by Folkman, and had additional anti-tumor properties. Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the therapeutic compositions of Folkman et al., comprising transformed cells and a matrix of collagen to place the transformed cells on the surface of a fibrous protein (e.g., matrix) as taught by Allen, particularly because Allen teaches and successfully exemplifies modified cells adhered to support matrices of collagen able to express a protein of interest at the desired site for therapeutic treatment. One of ordinary skill in the art, furthermore, would have expected Applicant's invention to perform equally well with cell preparations transformed with other base

sequences because the claimed transformed cell-containing preparations will have similar mechanical and biocompatibility properties. The references above provide all the elements of cells deposited on the surface of the fibrous protein to anticipate **claim 33.**

Claims 31 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., EP 1074264, Nakamura, T., WO 99/55361 and Seki et al. (Biochem. Biophys. Res. Commun. 172(1): 321-327, 1990; hereafter Seki-A) as applied to claims 30, 32, and 34-39 above and further in view of Medico et al., , US Patent US 6551991 (Date of Patent, April 22, 2003) and Junqueira et al., (Basic Histology, 1986, Lange Medical Publications, pp. 64-65).

The teachings of Folkman et al., Kuba et al. Nakamura, T. and Seki are outlined in the paragraph above. The combined references fail to teach that cells are epithelial cells of the oral mucosa.

However, at the time the invention was made, Medico et al., discloses recombinant proteins obtained from structural domains derived from the N-terminal hairpin domain and four-Kringle domains of HGF (col. 1, lines 49-54). Moreover, Medico et al., teaches that the mature (dimeric) form of the factor is able to activate its receptor at the surface of the target cells e.g., the Met tyrosine kinase/HGF receptor to mediate biological responses including cell proliferation preferentially on epithelia of different organs which are the target tissues of HGF (col.1, lines 64-67). Furthermore, Medico et al., teaches the most important target tissues of HGF are epithelia of different organs, such as liver, kidney, lung, breast, pancreas and stomach, and some cells of

the hematopoietic and nervous systems(col. 2; lines 10-15). Though Medico et al., does not particularly teach epithelial cells of the oral mucosa, the presence of epithelial cells in the digestive track was well known in the art as evidence by the teachings of Junqueira et al., (p. 65, col.2) .

Therefore, it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to have used a DNA encoding the human HGF/NK4(del 5) of Nakamura (i.e. instant SEQ ID NO: 4 encoded by instant SEQ ID NO: 2) as the anti-angiogenic factor in the cell method of Folkman et al., comprising transformed cells and a matrix of collagen. Kuba taught that human NK4 was structurally and functionally very similar to angiostatin, exemplified by Folkman, and like angiostatin, was an anti-angiogenic polypeptide. In addition to its anti-angiogenic properties, Kuba taught that NK4 was an antagonist of c-Met/HGF receptor, which activity may have been responsible for its activity in inhibiting metastasis. Nakamura taught that either of the two isoforms of human NK4, i.e. those of instant SEQ ID NOs: 1 and 2 were equivalents for use in inhibiting angiogenesis. Thus, Folkman, Kuba, and Nakamura, show that both NK4 isoforms are both structural and functional homologs to angiostatin, and additionally inhibit metastasis, possibly mediated by its antagonism of the c-Met/HGF receptor. The structural and functional similarity to angiostatin and additional antagonist activity would have suggested that the NK4 isoforms, including that of instant SEQ ID NO: 4 encoded by instant SEQ ID NO: 2, were suitable in the method taught by Folkman, and had additional anti-tumor properties. Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art, as a matter of design of choice, to use any cell comprising the Met tyrosine kinase/HGF receptor to mediate biological responses of the human HGF/NK4(del 5) (i.e. instant SEQ ID NO:

4 encoded by instant SEQ ID NO: 2) possibly because of by its antagonism of the c-Met/HGF receptor, including epithelial cells of the oral mucosa, particularly because Applicant has not disclosed that epithelial cells of the oral mucosa provide an advantage, is used for a particular purpose, or solves a stated problem. The manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art would have had a reasonable expectation of success in generating a method comprising an epithelial cell selected from the oral mucosa comprising a rAAV having a sequence set forth by SEQ ID no. 2 to achieve the predictable results of inhibiting metastasis of cancer or inhibiting angiogenesis by combining the detailed teachings of Folkman et al., Kuba et al. Nakamura, T. and Seki, Medico and of Junqueira. The references above provide all the elements of epithelial cells of the oral mucosa transformed with a rAAV to anticipate **claim 31 and 40.**

Conclusion

Claims 30-40 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any

inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633